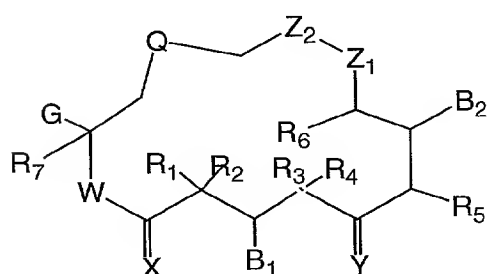


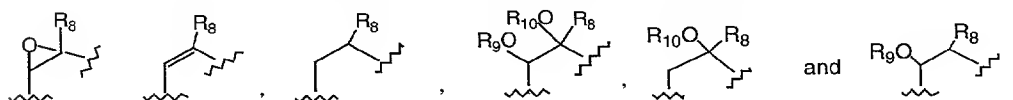
What Is Claimed Is:

1. A method for the treatment of proliferative
 5 diseases, including cancer, which comprises administering
 to a mammalian specie in need thereof a synergistically,
 therapeutically effective amount of (1) at least one
 anti-proliferative agent(s) and 2) a compound of formula
 I,

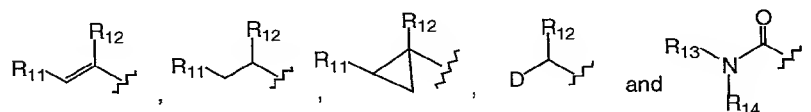


wherein:

15 Q is selected from the group consisting of



G is selected from the group consisting of alkyl,
 substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or N R₁₅;

X is O or H, H;

Y is selected from the group consisting of O; H, OR₁₆
 25 ; OR₁₇, OR₁₇; NOR₁₈; H, NHOR₁₉; H, NR₂₀R₂₁; H, H; and CHR₂₂;
 wherein OR₁₇, OR₁₇ can be a cyclic ketal;

Z₁ and Z₂ are independently selected from the group

consisting of CH_2 , O, NR_{23} , S, and SO_2 , wherein only one of Z_1 and Z_2 can be a heteroatom;

B_1 and B_2 are independently selected from the group consisting of OR_{24} , OCOR_{25} , and $\text{O}-\text{C}(=\text{O})-\text{NR}_{26}\text{R}_{27}$, and when B_1 is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of $\text{NR}_{28}\text{R}_{29}$, $\text{NR}_{30}\text{COR}_{31}$ and saturated heterocycle;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_{13} , R_{14} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{26} and R_{27} are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_9 , R_{10} , R_{16} , R_{17} , R_{24} , R_{25} and R_{31} are independently selected from the group consisting of H, alkyl, and substituted alkyl;

R_8 , R_{11} , R_{12} , R_{28} , R_{30} , R_{32} , and R_{33} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R_{15} , R_{23} and R_{29} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $\text{R}_{32}\text{C}=\text{O}$, R_{33}SO_2 , hydroxy, O-alkyl or O-substituted alkyl; and

pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1 , R_2 and R_7 are H; and

R_3 , R_4 and R_6 are methyl; and

R_8 is H or methyl; and

Z_1 and Z_2 are CH_2 ; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

and

Q is as defined above
are excluded.

5 2. The method according to Claim 1 wherein the
antiproliferative agent is administered following
administration of the Formula I compound.

3. The method according to Claim 1, wherein the
10 antiproliferative agent is administered prior to the
administration of the Formula I compound.

4. The method according to Claim 1 wherein the
15 antiproliferative agent is administered simultaneously
with the formula 1 compound.

5. The method according to Claim 1 for the treatment of
cancerous solid tumors.

20 6. The method according to Claim 1 for the treatment of
refractory tumors.

7. The method according to Claim 1 wherein the anti-
25 proliferative agent is selected from the group consisting
of a microtubule-stabilizing agent, a microtubule-
disruptor agent, an alkylating agent, an anti-metabolite,
epidophyllotoxin, an antineoplastic enzyme, a
topoisomerase inhibitor, procarbazine, mitoxantrone,
30 inhibitors of cell cycle progression, radiation and a
platinum coordination complex.

8. The method according to Claim 1 wherein the anti-
proliferative agent is selected from the group consisting
35 of an anthracycline drug, a vinca drug, a mitomycin, a

bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

5 9. The method according to Claim 1, wherein the Compound of Formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-
10 proliferative agent is Compound 2.

10. The method according to Claim 2, wherein the Compound of Formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
15 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

20 11. The method according to Claim 1, wherein the Compound of Formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-
25 oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

12. The method according to Claim 2 wherein said compound of Formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
30 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

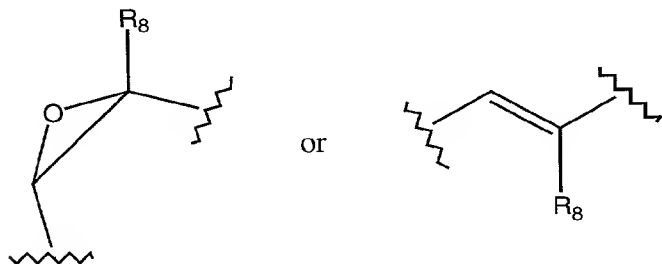
35

13. The method according to Claim 1 wherein said compound of Formula I is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.
14. The method according to Claim 2 wherein said compound of Formula I is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.
15. The method according to Claim 1, wherein said compound of Formula I is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.
16. The method according to Claim 3, wherein said compound of Formula I is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.
17. The method according to Claim 1, wherein said method comprises the administration of Compound 1 and Carboplatin.
18. The method according to Claim 1, wherein said method

comprises the administration of Compound 1 and doxorubicin.

19. The method according to claim 1, said method
5 comprising the administration of Compound 1 and CPT-11.

20. The method according to claim 1, wherein Q in said Formula I compound is



10

X is O;

Y is O;

Z₁ and Z₂ are, independently, CH₂; and

W is NR₁₅.

15

21. The method according to Claim 6, wherein said compound of Formula I is selected from the group consisting of:

20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-

pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

5 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

25 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-

8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
5 thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-1,5,5,7,9-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
20 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
25 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
30 pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
35 tetramethyl-16-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

5 [1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

10 [1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

15 [4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione; and pharmaceutically acceptable salts, solvates and hydrates thereof.

22. The method as claimed in Claim 7, wherein said Compound of Formula I is selected from the group consisting of:

- 5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-

pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

5 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

35 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
5 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-
5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
10 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-
5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
15 thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
20 thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
25 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

10 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-1,5,5,7,9-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-
20 dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-
dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-
25 dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
[4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-
5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-
cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-
30 5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-
16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-

thiazolyl)cyclopropyl]-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)cyclopropyl]-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
10 pentamethyl-16-[1-methyl-2-(2-hydroxymethyl- 4-
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;
and pharmaceutically acceptable salts, solvates and
hydrates thereof.

15 23. A pharmaceutical composition for the treatment
of cancer which comprises at least one anti-proliferative
agent and a compound of Formula I as described in Claim
1, and a pharmaceutically acceptable carrier.

20 24. The composition according to Claim 23 for the
treatment of cancerous solid tumors.

25 25. The composition according to Claim 23 for the
treatment of refractory tumors.

26. The composition according to Claim 23 wherein the
antiproliferative agent is one or more agent selected
from the group consisting of a microtubule-stabilizing
agent, a microtubule-disruptor agent, an alkylating
30 agent, an anti-metabolite, epidophyllotoxin, an
antineoplastic enzyme, a topoisomerase inhibitor,
procarbazine, mitoxantrone, inhibitors of cell cycle
progression, a platinum coordination complex, an
anthracycline drug, a vinca drug, CDK inhibitors, a
35 mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane,

compound 2, compound 3, an epothilone, discodermolide, a pteridine drug, a diyne, an aromatase inhibitor and a podophyllotoxin.

- 5 27. The composition according to Claim 23 wherein the compound of Formula I is selected from the group consisting of [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-
- 10 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-
- 15 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-
- 20 dione;
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-
- 25 dione;
- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-
- 30 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-
- 35 trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxo-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-

35

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
5 thiazolyl)ethenyl]-4-aza-17-
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-
10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-1,5,5,7,9-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-13-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-14-aza-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

15

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-
tetramethyl-16-[1-methyl-2-(2-methyl- 4-
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-
dione;

20

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-
dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

25

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-phenyl-7,11-
dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

30

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-
5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-
cyclohexadecene-16-carboxamide;

35

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-phenyl-4,8-dihydroxy-
5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-
16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)cyclopropyl]-4,17-

5 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-
thiazolyl)cyclopropyl]-4,17-

10 dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-16-[1-methyl-2-(2-hydroxymethyl- 4-
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;

15 and pharmaceutically acceptable salts, solvates and
hydrates thereof.

20 28. The composition according to Claim 26 wherein the
pharmaceutically acceptable salt is selected from the
group consisting of the hydrochloride salt, the
methanesulfonic acid salt and the trifluoroacetic acid
salt.

25 29. The composition according to Claim 26 wherein the
formula I compound is [1S-
1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-
thiazolyl)ethenyl]-4-aza-17-
30 oxabicyclo[14.1.0]heptadecane-5,9-dione or a
pharmaceutically acceptable salt thereof and the anti-
proliferative agent is Compound 2.

35 30. The composition according to Claim 26 wherein the
antiproliferative agent is Compound 3 and the formula I

compound is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-
 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-
 methyl-4-thiazolyl)ethenyl]-4-aza-17-
 oxabicyclo[14.1.0]heptadecane-5,9-dione or a
 5 pharmaceutically acceptable salt thereof.

31. The composition according to Claim 26 wherein the
 antiproliferative agent is Compound 5 and the formula I
 compound is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-
 10 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-
 methyl-4-thiazolyl)ethenyl]-4-aza-17-
 oxabicyclo[14.1.0]heptadecane-5,9-dione or a
 pharmaceutically acceptable salt thereof.

15 32. The composition according to claim 26 wherein the
 antiproliferative agent is cisplatin and the compound of
 formula I is [1S 1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-
 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-
 methyl-4-thiazolyl)ethenyl]-4-aza-17-
 20 oxabicyclo[14.1.0]heptadecane-5,9-dione.

33. The composition according to claim 23, wherein said
 composition comprises Compound 1 and carboplatin.

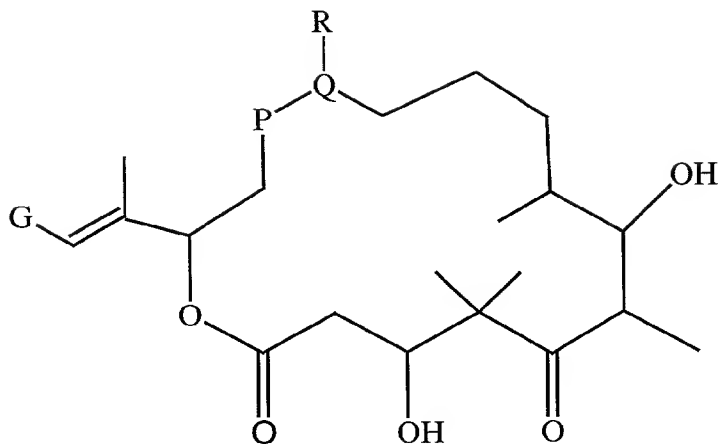
25 34. The composition according to claim 23, wherein said
 composition comprises Compound 1 and doxorubicin.

35. The composition according to claim 23, wherein said
 composition comprises Compound 1 and CPT-11.

30

36. A method for the treatment of proliferative
 diseases, including cancer, which comprises administering
 to a mammalian specie in need thereof a synergistically,
 therapeutically effective amount of (1) at least one
 35 anti-proliferative agent(s) and (2) a compound of Formula

II:

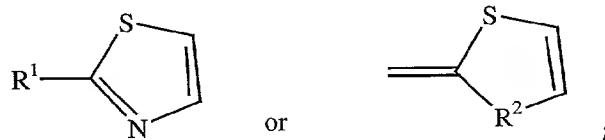


5

wherein:

P-Q is a C, C double bond or an epoxide;

G is

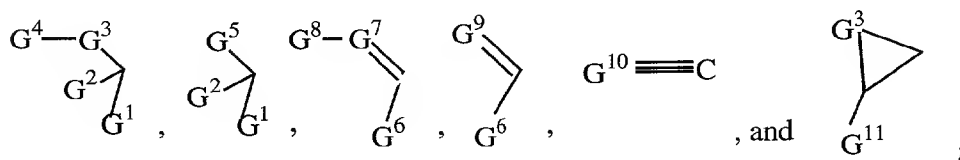


or

;

R is selected from the group of H, alkyl, and substituted alkyl;

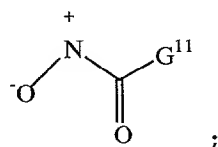
R¹ is selected from the group consisting of



, and

;

15

R² is

;

G¹ is selected from the group of H, halogen, CN, alkyl and substituted alkyl;

G² is selected from the group of H, alkyl, and

substituted alkyl;

G^3 is selected from the group of O, S, and NZ^1 ;

G^4 is selected from the group of H, alkyl, substituted alkyl, OZ^2 , NZ^2Z^3 , $Z^2C=O$, Z^4SO_2 , and optionally substituted glycosyl;

G^5 is selected from the group of halogen, N_3 , NCS, SH, CN, NC, $N(Z^1)_3^+$ and heteroaryl;

G^6 is selected from the group of H, alkyl, substituted alkyl, CF_3 , OZ^5 , SZ^5 , and NZ^5Z^6 ;

10 G^7 is CZ^7 or N;

G^8 is selected from the group of H, halogen, alkyl, substituted alkyl, OZ^{10} , SZ^{10} , $NZ^{10}Z^{11}$;

G^9 is selected from the group of O, S, -NH-NH- and -N=N-;

15 G^{10} is N or CZ^{12} ;

G^{11} is selected from the group of H_2N , substituted H_2N , alkyl, substituted alkyl, aryl, and substituted aryl;

Z^1 , Z^6 , Z^9 , and Z^{11} are independently selected from the group H, alkyl, substituted alkyl, acyl, and substituted acyl;

20

Z^2 is selected from the group of H, alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

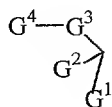
25 Z^3 , Z^5 , Z^8 , and Z^{10} are independently selected from the group H, alkyl, substituted alkyl, acyl, substituted acyl, aryl, and substituted aryl;

Z^4 is selected from the group of alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

30 Z^7 is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl, OZ^8 , SZ^8 , and NZ^8Z^9 ; and

Z^{12} is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, and substituted aryl;

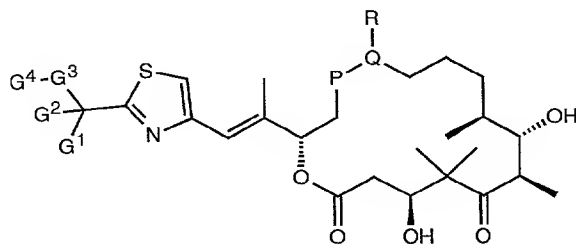
with the proviso that when R^1 is



G^1 , G^2 , G^3 and G^4 cannot simultaneously have the following meanings:

G^1 and $G^2 = H$, $G^3 = O$ and $G^4 = H$ or $Z^2C=O$ where $Z^2 =$
 5 alkyl group.

37. The method according to Claim 36 wherein the
 10 compound has the general formula IIa



where the symbols have the following meaning:

P-Q is a C,C double bond or an epoxide,

15 R is a H atom or a methyl group,

G^1 is an H atom, an alkyl group, a substituted alkyl group or a halogen atom,

G^2 is an H atom, an alkyl group or a substituted alkyl group,

20 G^3 is an O atom, an S atom or an NZ^1 group with Z^1 being an H atom, an alkyl group, a substituted alkyl group, an acyl group, or a substituted acyl group, and G^4 is an H atom, an alkyl group, a substituted alkyl group, an OZ^2 group, an NZ^2Z^3 group, a $Z^2C=O$ group, a Z^4SO_2
 25 group or an optionally substituted glycosyl group with Z^2 being a H atom, an alkyl group, a substituted alkyl group, an aryl group, a substituted aryl group or a heterocyclic group,

Z^3 an H atom, an alkyl group, a substituted alkyl group, an acyl group or a substituted acyl group, and Z^4 an alkyl, a substituted alkyl, an aryl, a substituted aryl or a heterocyclic group,

5

with the proviso that G^1 , G^2 , G^3 and G^4 cannot have simultaneously the following meanings: G^1 and G^2 = H atom, G^3 = O atom and G^4 = H atom or $Z^2C=O$ with Z^2 = alkyl group.

10 38. The method of claim 36 wherein said compound of Formula II is [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

15

39. The method according to Claim 36, wherein the antiproliferative agent is administered following administration of the Formula II compound.

20 40. The method according to Claim 36, wherein the antiproliferative agent is administered prior to administration of the Formula II compound.

41. The method according to Claim 36, wherein the
25 antiproliferative agent is administered simultaneously with the Formula II compound.

42. The method according to Claim 36 for the treatment of cancerous solid tumors.

30

43. The method according to Claim 36 for the treatment of refractory tumors.

44. The method according to Claim 36 wherein the anti-
35 proliferative agent is selected from the group consisting

of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

10

45. The method according to Claim 37 wherein the anti-proliferative agent is selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

20

46. The method according to Claim 36, wherein the Compound of Formula II is 1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

30

47. The method according to Claim 37, wherein the Compound of Formula II is 1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-

35

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

48. The method according to Claim 36 wherein said
 5 compound of Formula II is 1S-
 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-
 10 proliferative agent is Compound 3.

49. The method according to Claim 37 wherein said
 compound of Formula II is 1S-
 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
 15 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-
 proliferative agent is Compound 3.

20 50. The method according to Claim 36, wherein said
 compound of Formula II is 1S-
 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-
 25 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-
 proliferative agent is Cisplatin.

51. The method according to Claim 37, wherein said
 compound of Formula II is 1S-
 30 [1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-
 proliferative agent is Cisplatin.

35

52. The method according to Claim 36, wherein said compound of Formula II is 1S-

[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-

(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-

5 dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

53. The method according to Claim 37, wherein said

10 compound of Formula II is 1S-

[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-

(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-

dihydroxy-8,8,10,12,16-pentamethyl-4,17-

15 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

54. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and Carboplatin.

20

55. The method according to Claim 37, wherein said method comprises the administration of Compound 4 and Carboplatin.

25

56. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and doxorubicin.

57. The method according to Claim 37, wherein said method
30 comprises the administration of Compound 4 and doxorubicin

58. The method according to Claim 36, wherein said compound of Formula II is selected from the group
35 consisting of

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[[[(1,1-Dimethylethoxy) carbonyl] amino] methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-

15 dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-[[[(1,1-Dimethylethoxy) carbonyl] amino] methyl]-4-thiazolyl]-1-methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

20

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(pentanoyloxy) methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(naphthoyloxy) methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-[(2-methoxyethoxy)acetyloxy]methyl]-1-methyl-4-thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-(N-propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(3-Acetyl-2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

15

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-
tetraacetyl-alpha-glucosyloxy)methyl]-4-
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-
5 5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-
tetraacetyl-beta-glucosyloxy)methyl]-4-
10 thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-
5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-
15 glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-
20 toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
25 dihydroxy-8,8,10,12-tetramethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(5-Bromo-
2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-
30 8,8,10,12-tetramethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
35 dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[(phenylmethyl) imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[
 5 [[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-
 methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-
 4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
 8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-
 10 piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-4-[2-(7,11-
 Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-
 dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-
 15 thiazolecarboxylic acid;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-4-[2-(7,11-
 Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-
 dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-
 20 thiazolecarboxylic acid methyl ester;
 and the pharmaceutically acceptable salts, solvents and
 hydrates thereof.

59. A pharmaceutical composition for the pharmaceutical
 25 treatment of cancer with which comprises at least one
 anti-proliferative agent and a compound of Formula II as
 described in Claim 36, and a pharmaceutically acceptable
 carrier.

60. The composition according to Claim 59 for the treatment of cancerous solid tumors.

61. The composition according to Claim 59 for the treatment of refractory tumors.

62. The composition according to Claim 59 wherein the antiproliferative agent is one or more agent selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, a platinum coordination complex, an anthracycline drug, a cell cycle progression inhibitor, a vinca drug, a mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane, Compound 2, Compound 3, Compound 5, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

20

63. The composition according to Claim 59, wherein the compound of Formula II is selected from the group consisting of

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

- 5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
 [[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-
 thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-
 pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-
 dione;
- 10 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-[[[(1,1-
 Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-
 methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-
 oxa-13(Z)-cyclohexadecene-2,6-dione;
- 15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-(Aminomethyl)-4-
 thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-
 pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;
- 20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-
 [(pentanoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-
 [(naphthoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
 3-[2-[2-[(2-methoxyethoxy)acetyloxy]methyl]-1-methyl-4-
 thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
 8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-
 propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(3-Acetyl-
2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-
7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-
8,8,10,12-tetramethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-
(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-
dihydroxy-8,8,10,12,16-pentamethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
dihydroxy-8,8,10,12-tetramethyl-4,17-
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-
tetraacetyl-alpha-glucosyloxy)methyl]-4-
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-

30 5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-
tetraacetyl-beta-glucosyloxy)methyl]-4-
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-
tetraacetyl-beta-glucosyloxy)methyl]-4-
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-
5 5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-
glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
10 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-
toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
15 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
dihydroxy-8,8,10,12-tetramethyl-4,17-
20 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(5-Bromo-
2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-
8,8,10,12-tetramethyl-4,17-
25 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-
(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
dihydroxy-8,8,10,12,16-pentamethyl-4,17-
30 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-16-[2-[2-(Cyanomethyl)-4-
thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-
pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(phenylmethyl)imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-[[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid;

10

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid methyl ester

15 and the pharmaceutically acceptable salts, solvents and hydrates thereof.

20

64. The composition according to Claim 59 wherein the compound of Formula II is selected from the group consisting of

1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

25

65. The composition according to Claim 59 wherein the compound of Formula II is selected from the group consisting of

30

1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

35

66. The composition according to Claim 59 wherein said compound of Formula II is 1S-

[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-

5 dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

67. The composition according to Claim 59, wherein said

10 compound of Formula II is 1S-

[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-

dihydroxy-8,8,10,12,16-pentamethyl-4,17-

15 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.

68. The composition according to Claim 59, wherein said composition comprises Compound 4 and Carboplatin.

20 69. The composition according to Claim 59, wherein said method comprises the administration of Compound 4 and doxorubicin.

70. The composition according to Claim 59, wherein said
25 method comprises the administration of Compound 4 and CPT-11.